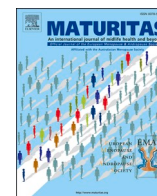




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## Is COVID-19 the worst pandemic?

Coronavirus disease 19 (COVID-19), the clinical disease caused by infection with the novel coronavirus SARS-CoV-2, has swept through countries around the world. With a few exceptions (mostly small island nations), every nation has been impacted by SARS-CoV-2 virus, making it a true pandemic disease.

Since the earliest recorded pandemic, which decimated Athens, North Africa and the Middle East in the years 429–426 BC (known as the Plague of Athens), and likely before, pandemic diseases have been some of the greatest challenges to humankind. The Plague of Athens resulted in 75–100,000 deaths, an estimated 25 % of the population at the time. What caused the Plague of Athens is not known; however, it is speculated that it may have been typhoid fever or Ebola. As the COVID-19 pandemic occupies global attention, the urge to compare it to outbreaks that have come before it is common. While availability heuristics caused by recency and intense media focus lead many to assume this is the worst pandemic there has ever been, more nuanced analysis reveals a complex picture that is highly dependent on context. At time of writing, SARS-CoV-2 has caused just over 100 million infections, and COVID-19 has been responsible for over 2.1 million [1] reported deaths; however, these numbers are certainly underestimated, due to differences in national reporting, health response, assignment of causality in the setting of comorbidity, and underreporting across large parts of the world [2]. While the number of fatalities is increasing rapidly, and the true toll of COVID-19 is unlikely to be known for many years, if ever, it is likely to remain lower than in many historical pandemics.

### 1. Coronaviruses

The COVID-19 pandemic is the third recorded outbreak of a coronavirus, with the 2002 sudden acute respiratory syndrome (SARS, SARS-CoV-1 or SARS-CoV) and the 2012 Middle East respiratory syndrome (MERS or MERS-CoV) epidemics preceding it. While these outbreaks are the easiest to directly compare virologically, the SARS-CoV-1 and MERS-CoV epidemics did not reach the global scale of COVID-19, for several reasons. Both SARS-CoV-1 and MERS-CoV have a higher case fatality rate (CFR) than COVID-19, indicating more deaths per number of infections. The SARS-CoV-1 virus (or SARS-CoV) caused 774 deaths from 8,096 reported cases between 2002 and 2004, with a CFR of 11 % [3], while the CFR for the MERS virus (or MERS-CoV) is greater than 35 %, with approximately 2,400 reported cases and 850 deaths [4]. The COVID-19 CFR is challenging to evaluate, due to widespread variability in public health response and capacity, availability of treatment, national demography, viral variants, and prevalence of comorbidities [5]. The mortality rate of COVID-19 is currently estimated to be between 2 % and 4 %; however, some countries have a CFR of less than 1 %, while

others (particularly poorer countries, and those whose healthcare systems have been overrun) have a CFR as high as 25 % [6]. While this makes SARS-CoV-2 a less lethal pathogen than the preceding coronaviruses that have seen outbreaks, it is far more widely spread. The 2002 SARS-CoV-1 epidemic is the most direct correlate for the current pandemic in terms of transmissibility; however, the rapid and highly coordinated health response limited the outbreak to a small number of cases in a small number of countries. The significantly more dangerous MERS-CoV has low levels of transmission, particularly from human to human in community transmission [7], which has significantly limited its impact globally. COVID-19's high transmissibility has made it of significant health concern. This is particularly relevant in at-risk patient demographics, where its CFR can increase to as much as 35 % in older people with comorbidities [8]. While SARS-CoV-1 and MERS are the microbes most closely associated with the current pandemic, more clinically relevant comparisons are likely found in the historical influenza pandemics (Fig. 1).

### 2. Influenza

The H1N1 influenza A pandemic of 1918–1920 (colloquially, but likely inaccurately, known as the Spanish flu) remains the deadliest pandemic of the modern age, with estimates of mortality ranging from 17 million to 100 million from an estimated 500 million infections globally (approximately a third of the global population at the time) over the three years from its initial outbreak [9]. In the light of vaccination programs and health responses internationally, it seems unlikely that COVID-19 will have the same impact on global health. However, poor accessibility and uptake of vaccines, and the rise of new variants, particularly in poorer nations, could lead to it becoming regionally endemic and significantly increase its impact over coming decades.

While these two pandemics are similar in scale, there are many contextual factors which lead to differences between the two. At the beginning of the H1N1 pandemic, scientific knowledge of viruses was in its infancy, and there were no specific treatments available. While public health measures such as quarantine of the ill, physical distancing, wearing of masks and, in some instances, border closures were enacted as we see today, these were inconsistent, and hampered by the ongoing World War I [9]. The war saw thousands of military personnel in confined spaces, often with poor hygiene standards, who would then carry the virus back to their home country, and other nations along transit routes. This led to a vast global spread of the virus and is thought to underpin its enormous impact [10]. The H1N1 virus also had a much shorter median incubation period than COVID-19, with infected individuals becoming symptomatic in 1–4 days (compared with

COVID-19's 5–6 days), meaning that it was able to spread more rapidly [11]. H1N1 was also particularly severe for an influenza, having a CFR of 2 %, compared with typical influenza infections of < 1 %, and was particularly lethal in young adults, who would typically be at lower risk [12]. This contrasts to the 2–4 % CFR of COVID-19, making it a slightly more fatal virus, despite all the advances of modern medicine. A more recent H1N1 (colloquially named 'swine flu') pandemic in 2009 had a far smaller impact than that of 1918, infecting approximately 700 million to 1.4 billion people (approximately 11–21 % of the world's population), but only causing an estimated 284,000 deaths, proportionally much lower than both the 1918 and COVID-19 pandemics [13], highlighting the importance of context when comparing these events. The availability of oseltamivir as a treatment for those infected with swine flu in 2009 and the availability of swine flu vaccine may have contributed to fewer fatalities in the 2009 pandemic.

### 3. Bubonic plagues

Historically, the most well-known and devastating pandemics were those of the bubonic plague. The first bubonic plague pandemic, known as the Plague of Justinian, was active for 21 years, 521 to 542 AD. It was first recorded in the Eastern Roman Empire (Byzantine Empire) and the Sassanian Empire; it spread between ports across the Mediterranean sea and into Asia Minor, Greece and Italy, resulting in 15–100 million deaths, when the estimated population of the world in 500AD was approximately 300 million. Hence, the first bubonic plague killed up to 30 % of the world's population.

The second bubonic plague, also known as the Black Death (caused by the flea-borne bacterium *Yersinia pestis*), which ravaged Europe, North Africa, and Asia from 1346 to 1353, is estimated to have caused up to 200 million deaths – as many as 60 % of the population of Europe at the time [14]. While these numbers are staggering, they are likely more reflective of the health knowledge of the time, rather than the infective properties of the microbes underlying them. The bubonic plague, named for its distinctive swollen lymph nodes or 'buboes', is still present in Asia, Africa and South America, with a handful of new cases every year (including a small number in the south-western US states) [15]. While the Black Death pandemic of 1346 was devastating, in modern times a parasite-borne infection is unlikely to generate widespread illness, due to improved hygiene standards. Additionally, *Yersinia pestis* is amenable to treatment with common antibiotics alongside supportive treatment.

The bubonic plague resurfaced in 1855 in an outbreak which lasted until 1960, known as the Third Plague. It originated in China and spread to Hong Kong and to port cities in the 1900s, including San Francisco, Oakland and the East Bay, and Los Angeles in 1924 and remained active until 1959, after which deaths decreased to fewer than 200 per year. The disease still affects rodents and can be transmitted from rodents to humans even today. In fact, modern outbreaks of the disease were seen in 1994 in India, in 2003 in Algeria [16], in 2006 in the Democratic Republic of Congo [17] and in 2008 and 2014 in Madagascar [18] but were limited 100–150 deaths.

One major factor which led to the enormous impact of the bubonic plagues was its extended duration. Typically, the respiratory infectious disease pandemics have lasted 2–3 years before being suppressed, whereas the second plague (the Black Death) persisted for eight years and the Third Plague for 105 years, accumulating an enormous toll on the civilization of the day. Given it is unlikely that COVID-19 will persist (at this scale) for so many years, it is again unlikely to have such a monumental impact.

### 4. HIV/AIDS

Another significant pandemic of the modern era which has been ongoing for 40 years is human immunodeficiency virus (HIV), which causes Acquired Immunodeficiency Syndrome (AIDS). While not described as a pandemic, but a global epidemic by the World Health Organization, HIV has affected all countries globally, and in parts of the world is still a major source of mortality. Since the first identified case of HIV was described in 1981, it has infected an estimated 75 million people, and caused at least 35 million deaths [19]. In 2019, approximately 38 million people were living with HIV, and 690,000 people died from the disease [20].

Medically, the COVID-19 and HIV pandemics are difficult to compare. HIV is a chronic, currently incurable infection, which reduces life expectancy considerably, while COVID-19 is acute and can be recovered from (though reports of 'long COVID' are becoming common, and the chronic impacts of infection need to be studied). This chronicity leads to a different health and economic impact, which is likely greater per patient, but spread over a more sustainable time frame which avoids some of the pressures on healthcare systems that have been characteristic of the COVID-19 pandemic. While currently incurable, treatments for HIV/AIDS are improving, and aggressive retroviral treatments can in large part restore life expectancy and quality of life, suppressing the

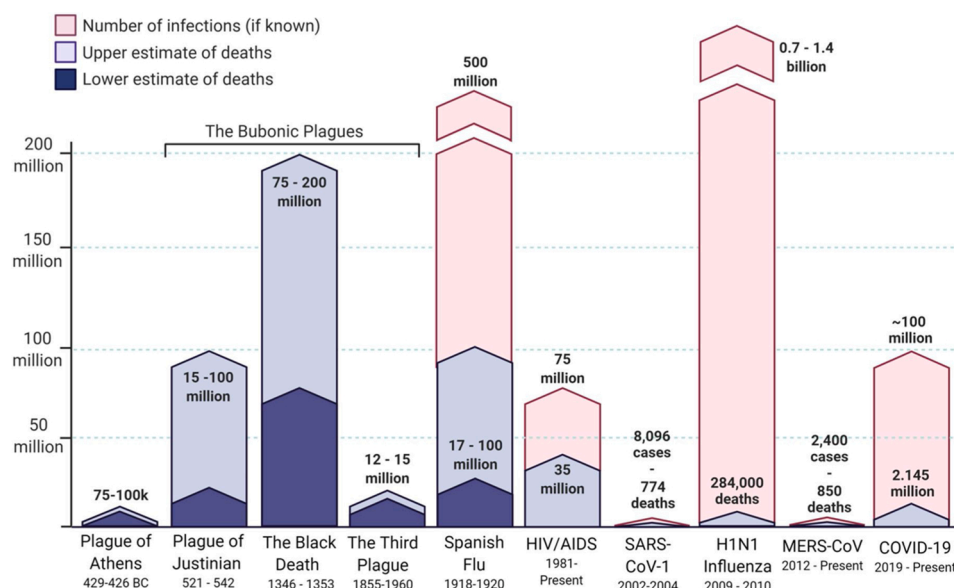


Fig. 1. A historical timeline of the major pandemics showing number of infections and upper and lower estimates of deaths.

virus to undetectable levels. Now that the underlying cause of HIV/AIDS is known, its transmissibility is significantly lower than that of the SARS-CoV-2 virus, as health awareness around barrier sexual prophylaxis and sharps hygiene has become more widespread [20]. However, even as rates of new infections are declining slowly, it is likely to be a global health challenge for years to come and will almost certainly amass more deaths than COVID-19.

## 5. Conclusion

While challenging to directly compare, it is likely that COVID-19 will not eventuate as the most damaging pandemic to society, both historically and in the modern age. The other pandemics discussed herein have had significant impacts on societies globally, with larger rates of infection and mortality. While these are all hugely context-specific to conditions, medical knowledge and health care responses, their ultimate impact on civilizations remains greater than that of COVID-19. In this editorial we have considered only the toll on human life and health, rather than the economic impacts of the disease, as these commonly are counter to healthcare objectives. Much of the undeniably vast cost of COVID-19 has come as a result of the action required to preserve life and health; however, it cannot be known what the price of inaction would be. As availability heuristics drive us to wonder whether this is the worst there has ever been, it is important to note the great success of public health responses globally, and to understand the enormous cost of past pandemics, next to which COVID-19 is small.

## Contributors

Jack Feehan contributed to the writing and revision of this editorial. Vasso Apostolopoulos conceptualized the editorial and contributed to the writing, revision and approval of the final version of this editorial.

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